

Prognostic Factors in Patients With Recurrent Differentiated Thyroid Carcinoma

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Background: Approximately 20% of patients with thyroid carcinoma have relapse. To evaluate the factors affecting their disease-free survival and prognosis, we studied 68 patients with recurrent differentiated thyroid carcinoma, ranging in age from 5 to 73 years (mean: 47.6 years). Three-fourths of patients were followed for >10 years. Thirty-nine patients were treated with total or subtotal thyroidectomy at first operation; the remainder underwent lesser operations. Fifty-six patients had local recurrence, mostly lymph node infiltration. Twenty-six patients died.

Methods: Survival curves were constructed using the Kaplan-Meier method. Factors affecting relapse and survival were tested by univariate or multivariate analysis.

Results: Univariate analysis identified age at diagnosis, local tumor extension, and surgical method as significant factors for disease-free survival. These three factors and histology were significant prognostic factors. Multivariate analysis showed age, histology, and disease-free interval as significant and independent variables.

Conclusions: In high-risk patients, complete resection of thyroid tissue and cervical lymph nodes is critical.

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Key words: thyroid cancer; prognostic factor; recurrence; disease-free survival; multivariate analysis

INTRODUCTION

In general, most patients with differentiated thyroid carcinoma are completely cured by their first operation [1,2]. Although ~20% of patients have recurrent tumor, long-term survival following relapse is common because tumor growth is very slow [3–5]. In some patients, however, the disease follows an aggressive course leading to cancer-related death [6]. Some institutes have recommended total thyroidectomy for most patients with thyroid carcinomas in spite of the low risk because high local recurrence rates in the contralateral lobe have been reported [7,8]. We have chosen surgical procedures based on the extent and stage of carcinomas as most institutes do, and we had 68 patients with relapse. To characterize the patients who eventually died of their

disease, we studied all patients with recurrent disease to evaluate risk factors at the time of recurrence.

MATERIALS AND METHODS

From 1972 to 1991, 68 patients had recurrent differentiated thyroid carcinoma in our hospital. All patients developed recurrence following resection of all macroscopic tumor. Recurrence of tumor was defined as an abnormality on follow-up physical examination, chest roentgenogram, or I¹³¹-scan. In our institute, total or sub-

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TABLE I. Recurrent, Differentiated Thyroid Carcinoma: Causes of Death

Cause	Number (N = 26)
Local recurrence	(%)
neck	8 (31)
mediastinum	5 (19)
Distance recurrence	
bone	6 (23)
lung	3 (12)
brain	2 (8)
liver	1 (4)
Cachexia	1 (4)

total thyroidectomy was performed in patients with thyroid carcinomas that were larger than one lobe size, multiple or bilobar, or in patients with palpable lymphadenopathy or macroscopic invasion to surrounding tissues. All other patients underwent lesser operations. We excluded patients with distant metastases or residual tumor in the neck at first operation. Patients with medullary carcinomas were excluded.

Statistics

Survival curves were constructed using the Kaplan-Meier method and analyzed using the log-rank test. Factors affecting disease-free survival were tested by univariate analysis. Multivariate analysis was performed according to Cox's proportional hazard model. Gender, age, tumor size, histology, surgical procedure, local tumor extension, lymph node metastases, local recurrence, distant metastases, operation time, and disease-free survival were tested as prognostic factors.

RESULTS

Patient Characteristics

There were 22 males and 46 females, ranging in age from 5 to 73 years at first operation (mean 47.6, median 50). The median follow-up of patients was 8 years and 76% (32/42 alive) of these patients were followed for >10 years. Twenty-six (38%) patients died. Thirteen (50%) died of locoregional failure (neck and mediastinum), and 12 patients (46%) died of distant metastases. The causes of death are listed in Table I. Among the patients who died, the median follow-up was 6 years (maximal follow-up, 34 years). Thirty-nine patients (57%) underwent total or subtotal thyroidectomy at first operation; the other 29 patients (43%) underwent lesser surgery. Fifty-six patients (82%) underwent two or more operations. Thyroidectomy for radioisotope treatment was not counted. Most patients (55/68, 81%) had lymph node metastases at first operation. Forty-three patients (63%) had some local invasion of muscle, carotid artery, trachea and/or larynx, recurrent laryngeal nerve, jugular vein, or esophagus. Histologic examination from the first

TABLE II. Differentiated Thyroid Carcinoma: First Recurrent Sites

Site	Number (N = 68)
Local	
neck	
lymph node	50
residual thyroid	5
mediastinum	1
Distant	
lung	7
brain	2
bone	1
Local & distant	2

operation showed papillary type in 60 patients (88%) and follicular type in 8 patients (12%).

With regard to initial recurrence sites, 55 patients (81%) had neck recurrence and 10 (15%) had distant metastases. First recurrence sites are listed in Table II. About one-half had relapse within 3 years. Fifty-one of 56 patients with local recurrence had lymph node infiltration, and the remaining five had relapse in residual thyroid tissues. Thirty-three patients eventually had distant metastases. Sites most frequently involved by distant metastases were the lungs and bone (Table III).

A comparison was made between patients who underwent total or subtotal thyroidectomy at first operation and patients who underwent lesser operations (Table IV). The former group had a shorter disease-free interval than the latter group. The distribution of disease-free interval of both groups is shown in Figure 1.

Prognostic Factors

The results of univariate analysis for risk factors are summarized in Table V. Age, surgical procedure, and local tumor extension were significant factors affecting disease-free interval. Age, histology, surgical procedure, and local tumor extension were also significant factors affecting survival. These four significant factors and disease-free survival were adopted for factors of Cox's proportional hazard model. Multivariate analysis clarified age, histology, and disease-free interval as significantly affecting survival (Table V). Survival curves are shown in Figure 2. Thirty-nine patients had whole body scan using radioiodine, and 27 of these were treated with therapeutic doses of ^{131}I . Radioiodine treatment did not improve survival (data not shown).

DISCUSSION

Some institutes have reported prognostic factors for thyroid carcinoma [9–11]. Prognostic factors reported by Hay et al. for papillary thyroid carcinoma were age at first operation (A), tumor grade (G), tumor extent (E), and tumor size (S), which were combined as the AGES

TABLE III. Recurrent Differentiated Thyroid Carcinoma: Site of Distant Metastases

Site	Number (N = 33) ^a
Lung	26
Bone	8
Brain	2
Skin	1
Liver	1

^aFive patients had distant metastases at two different sites.

TABLE IV. Comparison Between Patients Who Underwent Total or Subtotal Thyroidectomy at First Operation and Those With Lesser Operations

	Total or subtotal	Lesser operation
Age (mean + S.D., years)	50.2 + 18.3	44.1 + 15.9
Follow-up period (mean + S.D., years)		
total	9.4 + 5.9	18.8 + 10.0
dead	6.5 + 4.6	9.9 + 8.7
alive	11.9 + 5.7	20.9 + 9.8
Prognosis		
total	39	29
dead	18 (54%)	8 (28%)
alive	21 (46%)	21 (72%)
Disease-free interval (mean + S.D., years)	3.6 + 3.3	8.4 + 6.9

SD: Standard deviation.

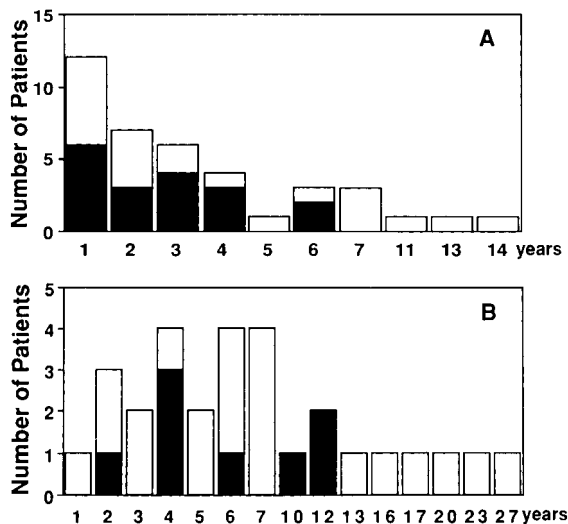


Fig. 1. The distribution of disease-free interval in patients who underwent total or subtotal thyroidectomy at first operation (A) or lesser operation (B). Closed parts indicate deaths. A. Relapse within 3 years occupied 60%, and death rate was high. B. Disease-free interval was widely distributed, and early death was rare, compared with A.

score (12). Cady et al. [13] separated patients into high- and low-risk groups, based on age (A), presence of distant metastases (M), size (S) and extent (E) of primary carcinomas. In our study, we focused on patients with recurrent thyroid carcinoma. Our analysis showed that

age and tumor extent were significant for survival, but tumor size and distant metastases were not. We performed total or subtotal thyroidectomy for larger tumors that might decrease the significance of size. Most patients had neck recurrence at first, and multivariate analysis showed that the disease-free interval was a significant prognostic factor. These results indicate that early relapse was closely associated with disease-death. Thus even if distant metastases are the first recurrence, if there is a long disease-free interval, death rate is low. Although 33 patients had distant metastases, local recurrence in 21 cases preceded distant metastases. These facts suggest the possibility that metastases derived from local recurrent tumors.

Our analysis showed that age, surgical procedure, and existence of local tumor extension are significant factors for disease-free survival and that patients who underwent total or subtotal thyroidectomy at first operation had shorter disease-free interval than those who had a lesser operation. Age is a common significant factor for relapse and survival. Surgical procedure is generally determined by degree of local tumor extension. Invasive carcinomas have high risk for microscopic residual tumor at operation and need wide resection.

In our study the most frequent site of first recurrence was the neck (Table II) and the most frequent sites of distant metastases were the lungs and bone (Table III). These findings are in agreement with those of previous studies [4,14,15].

Several reports propose that patients with follicular thyroid carcinoma have a poorer prognosis than ones with papillary thyroid carcinoma [1,16,17]. In our study, histology was a significant factor for survival by multivariate analysis, but not for disease-free interval by univariate analysis, although the number of patients with follicular carcinoma was small. This suggests that histology did not affect recurrence despite its importance as a prognostic factor.

Several studies regarding the influence of lymph node involvement on disease-free survival or prognosis in thyroid carcinoma have been reported. Some authors found no influence of node infiltration on prognosis in differentiated thyroid carcinoma [18]. However, latent cervical nodes at the time of diagnosis may be a risk factor [1,10]. In our study, regional lymph node involvement did not affect the development of recurrence or survival, although we did not assign grades of lymph node infiltration.

With regard to recurrence, Noguchi et al. [2] have reported that 75% of deaths or recurrences in patients with thyroid papillary carcinoma were within 10.4 years. Rossi et al. [11] have reported that >80% of recurrences occurred within 10 years. In our study, 92% of recurrence in patients who underwent total or subtotal thyroidectomy at first operation occurred within 10 years. By con-

TABLE V. Factors Affecting Disease-free Interval and Survival in Univariate and Multivariate (Cox proportional hazards model) Analysis of Thyroid Cancer

Factor	No. of patients	Disease-free interval	Survival	Survival	Risk ratio
		Univariate <i>P</i> value	Univariate <i>P</i> value	Multivariate <i>P</i> value	
Gender		0.0696	0.7307		
males	22				
female	46				
Age (years)		0.0006	0.0043	0.0007	1.078 ^a
<50	37				
≥50	31				
Tumor size		0.1343	0.0815		
<4 cm	36				
≥4 cm	32				
Histology		0.7068	0.0112	0.0177	3.704
papillary	60				
follicular	8				
First surgical procedure		0.0002	0.014	0.9371	0.952
total or subtotal	39				
lesser	29				
Local tumor extension		0.0412	0.0133	0.933	0.939
no	25				
yes	43				
Lymph node metastases		0.0833	0.2387		
no	13				
yes	55				
Distant metastasis		0.6983	0.0875		
no	35				
yes	34				
Operation time		0.8639	0.8047		
1 or 2 times	41				
≥3 times	27				
Disease-free interval				<0.0001	0.699

^a Risk ratio for increase of one year in age.

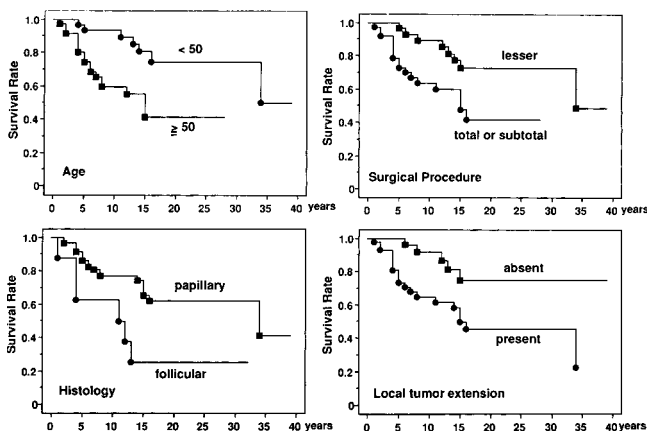


Fig. 2. Survival curves related to age, histology, local recurrence, and distant metastasis.

trast, 72% of recurrences following lesser operations occurred within 10 years. One-half of patients died of local control failure, and one-half died of distant metastases, but local failure usually occurred prior to distant metas-

tases. Most local recurrences were considered to be lymph node infiltration; local recurrence can be controlled by surgery. For high-risk relapsed patients, i.e., older age and shorter disease-free interval, complete resection of cervical lymph nodes at second operation may prevent distant metastases and improve survival.

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The first and second authors contributed equally to this work.

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